

LONDON  
SCHOOL of  
HYGIENE  
& TROPICAL  
MEDICINE



Pocock, SJ; Huo, Y; Van de Werf, F; Newsome, S; Chin, CT; Vega, AM; Medina, J; Bueno, H (2017) Predicting two-year mortality from discharge after acute coronary syndrome: An internationally-based risk score. *European heart journal Acute cardiovascular care*. p. 2048872617719638. ISSN 2048-8726 DOI: <https://doi.org/10.1177/2048872617719638>

Downloaded from: <http://researchonline.lshtm.ac.uk/4189938/>

DOI: [10.1177/2048872617719638](https://doi.org/10.1177/2048872617719638)

#### Usage Guidelines

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact [researchonline@lshtm.ac.uk](mailto:researchonline@lshtm.ac.uk).

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

# **Predicting Two-Year Mortality from Discharge after Acute Coronary Syndrome: An Internationally-Based Risk Score**

**Stuart J Pocock, MSc, PhD<sup>\*1</sup>, Yong Huo, MD<sup>2</sup>, Frans Van de Werf, MD, PhD<sup>3</sup>, Simon Newsome, MSc<sup>1</sup>, Chee Tang Chin, MBChB<sup>4</sup>, Ana Maria Vega, MD<sup>5</sup>, Jesús Medina, PhD<sup>5</sup>, Héctor Bueno, MD, PhD<sup>6,7</sup>**

*<sup>1</sup>London School of Hygiene and Tropical Medicine, London, UK; <sup>2</sup>Peking University First Hospital, Beijing, China; <sup>3</sup>Department of Cardiovascular Sciences, University of Leuven, Belgium; <sup>4</sup>National Heart Centre Singapore, Singapore; <sup>5</sup>Medical Evidence and Observational Research, Global Medical Affairs, AstraZeneca, Madrid, Spain; <sup>6</sup>Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain; <sup>7</sup>Instituto de investigación i+12 and Cardiology Department, Hospital Universitario 12 de Octubre, Madrid, Spain.*

## **Address for correspondence:**

Stuart Pocock, PhD, Professor of Medical Statistics,  
London School of Hygiene and Tropical Medicine,  
Keppel Street, London WC1E 7HT, United Kingdom.  
Tel: +44 (0)20 7927 2413; Fax: +44 (0)20 7637 2853  
Email address Stuart.Pocock@lshtm.ac.uk

**Word count:** 5,800

**Short title:** Two-year mortality risk prediction in ACS

## Abstract

**BACKGROUND:** Long-term risk of post-discharge mortality associated with acute coronary syndrome (ACS) remains a concern. The development of a model to reliably estimate 2-year mortality risk from hospital discharge post-ACS will help guide treatment strategies.

**METHODS:** EPICOR (long-term follow up of antithrombotic management patterns in acute CORonary syndrome patients, NCT01171404) and EPICOR Asia (EPICOR Asia, NCT01361386) are prospective observational studies of 23,489 patients hospitalized for an ACS event, who survived to discharge and were then followed up for 2 years. Patients were enrolled from 28 countries across Europe, Latin America, and Asia. Risk scoring for 2-year all-cause mortality risk was developed using identified predictive variables and forward stepwise Cox regression. Goodness-of-fit and discriminatory power was estimated.

**RESULTS:** 5.5% of patients died within 2 years of discharge. We identified 17 independent mortality predictors: age, low ejection fraction, no coronary revascularisation/thrombolysis, elevated serum creatinine, poor EQ-5D score, low haemoglobin, previous cardiac or chronic obstructive pulmonary disease, elevated blood glucose, on diuretics or an aldosterone inhibitor at discharge, male sex, low educational level, in-hospital cardiac complications, low BMI, STEMI diagnosis, and Killip class. Geographic variation in mortality risk was seen following adjustment for other predictive variables. The developed risk-scoring system provided excellent discrimination ( $c$ -statistic=0.80, 95% CI=0.79–0.82) with a steep gradient in 2-year mortality risk: >25% (top decile) vs. ~1% (bottom quintile). A simplified risk model

with 11 predictors gave only slightly weaker discrimination ( $c$ -statistic=0.79, 95% CI =0.78 to 0.81).

**CONCLUSIONS:** This risk score for 2-year post-discharge mortality in ACS patients ([www.acsrisk.org](http://www.acsrisk.org)) can facilitate identification of high-risk patients and help guide tailored secondary prevention measures.

## Introduction

There is still much variability in long-term prognosis for patients who present with an acute coronary syndrome (ACS) and survive to discharge from hospital.<sup>1</sup> After leaving hospital, risk from further ischemic events and death is compounded by high variability in secondary prevention measures both at-discharge and subsequently.<sup>2-4</sup> Hospital discharge therefore represents a crucial point for the assessment of individual patient risk and the adoption of appropriate management strategies, including advice to the patient.<sup>5,6</sup> The ability to identify those patients with poor prognosis on leaving hospital could potentially guide optimal patient management.

There are several reports on the use of risk scoring methods in ACS with a few large-scale observational studies having identified predictors of mortality following an ACS event.<sup>7,8</sup> Most notable are the Global Registry of Acute Coronary Events (GRACE) risk scores,<sup>9</sup> although these focus mainly on risk from time of hospital admission and, as such, represent a different scenario. Additionally, Eagle et al<sup>10</sup> provide a risk model for post-discharge mortality, albeit with follow-up of only 6 months. We previously examined 10,567 patients with ACS from Europe and Latin America in the EPICOR (long-term follow up of antithrombotic management patterns in acute CORonary syndrome patients) study<sup>11</sup> and established a reliable risk-scoring tool for evaluating 1-year post-discharge mortality risk.<sup>12</sup>

Data are now available up to 2-years post-discharge in a larger patient population including both the EPICOR and the EPICOR Asia (n=12,922 patients)<sup>13</sup> studies. Assessment of risk based on this increased sample size will provide increased predictive reliability and generalizability to different geographic regions

and healthcare systems. The aim is to explore relationships between patient demographics, medical history and management from data collected during admission, hospitalization, and at discharge, and subsequent 2-year mortality, thereby facilitating the development of a reliable and user-friendly risk-scoring system for individual patient 2-year survival.

## Methods

EPICOR and EPICOR Asia are prospective, international cohort studies of unselected populations comprising consecutive patients hospitalized for an ACS event (ST-segment elevation myocardial infarction [STEMI], and non-ST-segment elevation myocardial infarction or unstable angina [NSTEMI/UA]) either within 24 h (EPICOR) or 48 h (EPICOR Asia) of symptom onset, and who survived to hospital discharge.

Follow-up data were available for 23,489 patients enrolled from 774 hospitals in 28 countries (EPICOR, 10,567 patients from 555 hospitals in 20 countries across Europe and Latin America; EPICOR Asia, 12,922 patients from 219 hospitals across 8 countries and regions in Asia). The primary aim of these studies was to describe the frequency of different short- and long-term anti-thrombotic management patterns (AMPs) for patients with an ACS, both during hospitalization for the index event and after hospital discharge (up to 2 years) in a wide range of hospitals and countries. In addition, relationships between AMPs used and clinical outcomes were evaluated. The protocol and case record forms of both EPICOR and EPICOR Asia are almost identical and detailed accounts of the methodologies of both studies are described elsewhere.<sup>11, 13-15</sup> In brief, the National Coordinator in each country was responsible for site selection and, based on comprehensive lists of hospitals, defined the proportion of patients treated at hospitals with and without invasive cardiac intervention facilities, thus ensuring a fair representation of real-life practice at a country level. Each participating site completed a questionnaire to provide information on key site characteristics and aimed to enrol at least 10 consecutive

patients; enrolled at the point of hospital discharge. Eligible patients were required to provide written informed consent, and agree to be contacted by telephone for regular follow-up interviews during the post-discharge phase. All data were collected using electronic case report forms, set-up and managed by the AstraZeneca Data Management Hub in Sweden. The final protocol for each study was approved by the applicable ethics committee from each country, and each was performed in accordance with ethical principles consistent with the Declaration of Helsinki revision, the International Conference on Harmonization Good Clinical Practice guideline, and applicable legislation on non-interventional studies.

## **Statistical Methods**

In total, 55 candidate variables were identified as potential predictors based on data collected during admission, hospitalization, and at discharge relating to patient demographics, medical history and other relevant information (see Appendix Table 1). Using Cox proportional hazard models with forward stepwise variable selection (employing  $P < .01$  as a criterion for variable inclusion) an initial risk model for 2-year mortality was developed.

Further analyses were undertaken to ensure assumptions of the model were not violated, for example potential non-linearity of prediction, and the model refined accordingly. Additionally, Schoenfeld residuals were used to test the proportional hazards assumption of every variable included in the final model and, based on this, there was no evidence the assumption was violated for any variable.

As a result, some continuous predictors were remodelled either with a binary cut-off point e.g., for body mass index (BMI) and haemoglobin, or expressed as a



linear trend only above a certain threshold e.g., for creatinine and blood glucose. Separate risk models for NSTEMI-ACS and STEMI patients were explored, but showed no evidence of interactions. We did not explore potential statistical interactions between predictor variables because the large number of such analyses would facilitate identification of false positive findings.

To allow for prognostic variables having some missing data (Table 1) multiple imputation was used in the final model to avoid unnecessary loss of observations.<sup>16</sup> For continuous variables, the transformation then imputation method of Von Hippel<sup>16</sup> was used to aid in deriving reliable risk estimates. While most identified predictor variables are familiar, one valuable addition is the EuroQoL (EQ-5D) patient questionnaire.<sup>17</sup> Using the EQ-5D, the patient graded each of five parameters i.e., mobility, self-care, ability to perform usual activities, pain/discomfort, and anxiety/depression as 'no problem' (0 points), 'moderate' (1 point), or 'a severe limitation' (2 points). Avoiding the use of complex weighted schemes, we provide a simple overall score (0 to 10 points) to facilitate user-friendly risk prediction.

The Nam-D'Agostino test<sup>18</sup> was used to assess goodness-of-fit in comparing observed- vs. model-derived mortality risk.

The model was internally validated using a bootstrap method, as opposed to data-splitting, to estimate the discriminative ability of the model when used on external data.<sup>19</sup> Use of the bootstrap method has been shown to have comparable accuracy to external validation<sup>20, 21</sup> and avoided the loss of valid data for the model building phase.

All analyses were performed using Stata 14.0.

## Results

The study cohort comprised a total of 23,489 consecutive patients presenting with an ACS event who survived to hospital discharge (EPICOR n=10,567; EPICOR Asia n=12,922). Mean age was 60.9 years, 24% were female, and 14% had had a prior myocardial infarction. Within 2 years following hospital discharge, 5.5% of patients (n=1,282) had died. Overall, 13.7% of patients did not achieve 2 years of follow-up, but 75% of these had more than 1 year of follow-up. Hence, the total patient years of lost follow-up was 6.0%.

Forward stepwise Cox proportional hazard modelling identified 17 independent ( $P<.005$ ) predictors of 2-year mortality risk. Table 1 provides descriptive statistics for these 17 predictors overall, and by study and by patient diagnosis (STEMI or NSTEMI-ACS). Of the latter, 55% were declared NSTEMI and 45% unstable angina. Table 2 summarizes the multivariable risk model with hazard ratio (HR) and 95% confidence interval (CI) for each independent predictor. Variables are listed in order of statistical strength of prediction based on multiple imputation to overcome the issue of missing data.

The predictors in order of predictive strength were: age, low ejection fraction, no coronary revascularisation or thrombolysis performed, raised serum creatinine, poor EQ-5D score, low haemoglobin, previous cardiac disease, previous chronic obstructive pulmonary disease (COPD) or other chronic lung disease (CLD), and raised blood glucose (each  $P<.00001$ ). Other independent predictors were use of either a diuretic or an aldosterone inhibitor at discharge, male sex, low educational

level, in-hospital cardiac complications, low BMI, diagnosis of STEMI, and Killip class >I.

When patients diagnosed with STEMI and NSTEMI-Acute Coronary Syndrome (ACS) were analyzed separately all other predictors showed a similar impact on mortality risk in the two risk models (Table 3). Note, in univariate analysis (Table 1), STEMI patients were observed to have a lower 2-year mortality than NSTEMI-ACS patients (5.0% vs 5.9%) but the latter had a poorer risk profile in regard to other key predictors such as age. Thus, after multivariable adjustment STEMI diagnosis was seen to independently contribute to a higher mortality risk (HR 1.22 vs NSTEMI-ACS). Based on evidence of non-linearity in survival prediction, the impact of increased serum creatinine on mortality was confined to those with levels  $\geq 1.2$  mg/dL. Similarly, cut-off levels  $\geq 140$  mg/dL,  $< 13$  g/dL, and  $< 20$  kg/m<sup>2</sup> were used for blood glucose (linear), haemoglobin (categorical), and BMI (categorical), respectively.

The estimated impact of each predictor on mortality risk from the overall model in Table 2 is visually illustrated in Figure 1. Notable increases in mortality risk were evident for increasing age, serum creatinine, blood glucose, Killip class, and EQ-5D score and reduced risk with increasing haemoglobin, BMI, and improved educational level. Further independent predictors of increased mortality risk were; low ejection fraction, no coronary revascularisation or thrombolysis during admission, in-hospital cardiac complications, previous cardiac disease, previous COPD/other CLD, and male sex. In addition, substantial regional differences in 2-year mortality risk persisted after adjustment for other predictors. For example, with China as the reference country, Northern Europe region, as well as Hong Kong, Singapore, and

South Korea combined had the lowest risk (HR 0.72 and 0.60, respectively) while Latin America and Eastern Europe had the highest risk (HR 1.44 and 1.24, respectively).

A risk score is calculated for each patient from the risk coefficients of the linear predictors for the overall model (Table 2). The 2-year mortality risk for each individual is  $1 - 0.99842^{\exp(\text{risk score})}$ . Figure 2A shows the distribution of individual scores for all 23,489 patients along with the relationship between patient risk score and the probability of dying within 2 years of discharge. Patients were stratified into 6 risk groups; groups 1–4 representing the first four quintiles of patients and groups 5 and 6 representing the top 2 deciles of risk. Figure 2B shows the relationship between such risk groups and cumulative mortality over 2 years. From these data there is a marked discrimination in mortality across the risk groups. For example, comparing extremes, the top decile (group 6) had a 2-year mortality risk greater than 25% whereas the bottom quintile (group 1) had a 2-year mortality risk around 1%.

In addition to good discrimination between risk groups, measures of goodness-of-fit comparing observed- vs. model-predicted 2-year mortality rates based on the Nam-D'Agostino test showed strong similarities between observed and predicted mortality ( $P=.12$ ) i.e., the model provided a good fit of the data across mortality risk groups (Figure 2C). In addition, discrimination of the model was found to be very good ( $c$ -statistic=0.80, 95% CI=0.79–0.82). The bootstrap validation method estimated only a very small degree of bias due to overfitting; overall, 800 resamples provided an estimated bias of 1.2% (95% CI=0.06%–3.2%) suggesting

Harrell's *c* statistic, if the model was used on new, external data, would be 0.798 (95% CI=0.788–0.803).

To facilitate the practical use of our risk model, we have developed a more simplified version. This has been achieved by removal of six of the variables which had a somewhat lesser impact on patient risk. The variables removed were: on diuretics and on aldosterone inhibitor at discharge, education level, in-hospital complications, body mass index, and Killip class. The results for this simplified risk model (with just 11 predictive variables) are provided in Appendix Table 2 and Appendix Figure 1. The model fit remained good, and discriminatory power was only slightly reduced (*c*-statistic=0.79, 95% CI=0.78-0.81).

## Discussion

Based on patient data combined from EPICOR and EPICOR Asia,<sup>11, 13</sup> two large international prospective cohort studies of unselected populations involving more than 23,000 patients hospitalized and discharged following an ACS event, we were able to identify 17 highly independent predictors of mortality during the 2-year period following hospital discharge. The combining of patient data from these large very similar studies provided a unique opportunity to reliably quantify long-term individual patient risk post discharge based on representative populations across Europe, Latin America, and Asia in a variety of healthcare systems. Moreover, the fact that all risk predictors identified are conducive to ready quantification/collation in routine clinical practice, provided the opportunity for us to create a web-based risk calculator ([www.acsrisk.org](http://www.acsrisk.org)) to facilitate risk prediction for future patients.

Age, low ejection fraction, lack of use of coronary revascularisation or thrombolysis, previous COPD/other CLD, along with raised serum creatinine, raised glucose and low haemoglobin levels in blood samples obtained at admission each made major contributions to increased mortality risk. The significant effects of previous COPD/other CLD, low haemoglobin and raised blood glucose<sup>22</sup> confirm that non-cardiac conditions do convey a mortality risk in ACS patients.

The increased risk associated with no coronary revascularisation/thrombolysis could mirror risk/benefit analysis and selection strategies against providing such intervention in patients with an anticipated poor prognosis post-discharge.<sup>23</sup> The marked contribution from patient-reported quality of life at discharge, based on a simplified scoring system applied to the EQ-5D questionnaire<sup>17</sup> indicates how poor

functional quality of life at discharge reflects other factors that impact on mortality risk in ways not captured by other predictors such as frailty,<sup>24</sup> depression or other comorbidities. Although in univariate analysis (Table 1) men had a lower 2-year mortality risk than women (5.1% vs 6.6%), in the multivariable model accounting for other risk factors (e.g., age at presentation), male sex independently predicted a 32% higher risk. Similarly, STEMI patients overall had a lower 2-year mortality than NSTEMI-ACS patients (5.0% vs 5.9%, respectively) but, after adjustment for other predictors, STEMI diagnosis carried an independent 22% higher risk suggesting that the poor prognosis of NSTEMI-ACS was largely driven by older age and comorbidities while the consequences of STEMI as such were worse probably driven by significant myocardial damage.

As expected, most patients could be classified as low risk with approximately half of patients having a 2-year mortality risk <3%. Only 13% had a 2-year risk >10% while 5% had a risk >20%. This is relevant as it may become a clinically useful tool to select the patients needing more aggressive secondary prevention strategies.<sup>25</sup> Close agreement was evident between observed and predicted 2-year mortality rates across risk groups confirming a good model fit of the data.

In general, our findings for 2-year mortality post discharge complement those reported from EPICOR up to 1-year post discharge.<sup>12</sup> The overall mortality rate at 2-years post-discharge was 5.5% compared with 3.9% after 1-year. We have now identified 17 highly predictive variables on 2-year follow-up compared with 12 previously. The six new predictors are: no coronary revascularisation or thrombolysis performed, previous cardiac disease, aldosterone inhibitor use at discharge,

education level, diagnosis (STEMI), BMI ( $<20 \text{ kg/m}^2$ ), and Killip class. Note, a higher mortality of underweight patients with coronary artery disease has been previously reported.<sup>26</sup> One predictor of 1-year mortality, peripheral vascular disease, was no longer evident at 2 years.

There is an extensive literature on the use of risk scores in ACS.<sup>8</sup> However, for predicting longer-term mortality, the choice is somewhat limited, with the GRACE Registry representing the most widely used risk score.<sup>9, 27</sup> However, the emphasis of GRACE is on prediction from hospital admission, which inherently includes substantial in-hospital mortality risk. Our focus is on prognosis from the moment of hospital discharge; an appropriate timing when strategies for future patient management are determined.

Analogous to our intent, Eagle et al<sup>10</sup> have used the GRACE Registry to develop a prediction model for 6-month post-discharge mortality. Based on nine predictor variables (age, history of heart failure, history of myocardial infarction, heart rate, systolic blood pressure, ST-segment depression, serum creatinine, elevated cardiac enzymes, and no in-hospital percutaneous coronary intervention) they achieve good discrimination;  $c=0.81$  and  $0.75$ , respectively in development and validation cohorts. However, 6 months' follow-up might be considered too short and a longer-term perspective is needed when linking prognosis to patient management. The latest GRACE models<sup>9</sup> do include post-discharge prediction out to 3 years but have two limitations: only data collected at admission are used, and survival data beyond 1 year is confined to a UK cohort of 1,274 patients.



The presence of substantial geographic variations in 2-year mortality risk, even after adjustment for the 17 predictors identified in our model, is highly relevant given widely acknowledged between-country variability in patient management, and the fact this reported risk-scoring model is based on one of the widest ACS cohorts ever compiled globally. Further study into the reasons for this variability is warranted.

Several potential limitations should be noted for the present analysis. There is no external validation of the risk model and, being a study on hospital survivors, blood pressure and heart rate at admission were not recorded, and some in-hospital complications (bleeding, stroke, infection) were not included in the model. It was considered a better approach to utilize the entire two cohorts comprising more than 23,000 patients and 1,292 deaths, and then employ the bootstrap method of internal validation. Although STEMI and NSTEMI-ACS events might be considered sufficiently different to require development of two separate risk models, we considered this was not necessary given the substantial consistency of risk prediction post-discharge across these two event types (Table 3). The possibility exists for inclusion of false positive predictor(s) given more than 50 candidate variables were considered initially, but the use of  $P < .01$  as an entry criterion should minimise this risk. Moreover, as for any observational study, caution must be expressed in extrapolating findings to the overall patient population. Since a model with 17 variables may be considered large for practical use, we have also presented a simplified model with just 11 predictive variables. This led to only a very modest loss in discriminatory power. It would be of interest to extend our work to predict non-fatal ischaemic events and, specifically, cardiovascular death, but this is hampered by less reliable data capture compared to the focus on all-cause death. The patient-

years of loss to follow up (6%) is a limitation but is sufficiently modest to not seriously affect the reported findings from this large international cohort study.

In conclusion, this analysis demonstrates that ACS-related mortality risk up to 2-years following hospital discharge can be reliably estimated based on 17 highly predictive variables, each of which can be readily recorded at hospital discharge. Risk discrimination and model fit are good, and use of our easy-to-use risk-scoring algorithm (both full and simplified versions are available at [www.acsrisk.org](http://www.acsrisk.org)) will aid identification of those patients with relatively poor prognosis at discharge, and may potentially guide tailored secondary prevention measures to improve prognosis in the longer term.

## **Acknowledgments**

EPICOR and EPICOR Asia are funded by AstraZeneca. Being a non-interventional study, no drugs were supplied or funded. Professor Pocock had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Editorial support was provided by Carl V Felton PhD of Prime Global (Knutsford, Cheshire, UK), funded by AstraZeneca.

## Disclosures

**S. Pocock** has received research funding from AstraZeneca; **Y. Huo** has nothing to disclose; **F. Van de Werf** has received consulting fees and research grants from Boehringer Ingelheim and Merck, and consulting fees from Roche, Sanofi-Aventis, AstraZeneca, and The Medicines Company; **S. Newsome** has nothing to disclose; **C.T. Chin** has received research support from Eli Lilly; honoraria from Medtronic, and has been a consultant or advisory board member for AstraZeneca; **A. Vega** and **J. Medina** are employees of AstraZeneca; **H. Bueno** has received advisory/consulting fees from Abbott, AstraZeneca, Bayer, BMS, Daichii-Sankyo, Eli-Lilly, Menarini, Novartis, Pfizer, Sanofi, and Servier, and grants from AstraZeneca.

## References

1. Fox KAA, Carruthers KF, Dunbar DR, Graham C, Manning JR, De Raedt H, Buysschaert I, Lambrechts D, Van de Werf F. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). *Eur Heart J* 2010;31:2755-2764.
2. Menzin J, Wygant G, Hauch O, Jackel J, Friedman M. One-year costs of ischemic heart disease among patients with acute coronary syndromes: findings from a multi-employer claims database. *Curr Med Res Opin* 2008;24:461-468.
3. Huo Y, Thompson P, Buddhari W, Ge J, Harding S, Ramanathan L, Reyes E, Santoso A, Tam LW, Vijayaraghavan G, Yeh HI. Challenges and solutions in medically managed ACS in the Asia-Pacific region: expert recommendations from the Asia-Pacific ACS Medical Management Working Group. *Int J Cardiol* 2015;183:63-75.
4. Chan MY, Du X, Eccleston D, Ma C, Mohanan PP, Ogita M, Shyu KG, Yan BP, Jeong YH. Acute coronary syndrome in the Asia-Pacific region. *Int J Cardiol* 2015;202:861-869.
5. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835-842.

6. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation* 2000;101:2557-2567.
7. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999-3054.
8. Bueno H, Fernandez-Aviles F. Use of risk scores in acute coronary syndromes. *Heart* 2012;98:162-168.
9. Fox KAA, Fitzgerald G, Puymirat E, Huang W, Carruthers K, Simon T, Coste P, Monsegu J, Gabriel Steg P, Danchin N, Anderson F. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open* 2014;4:e004425.
10. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA. A validated prediction model for all forms of acute coronary syndrome:

estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004;291:2727-2733.

11. Bueno H, Danchin N, Tafalla M, Bernaud C, Annemans L, Van de Werf F. EPICOR (long-term follow-up of antithrombotic management Patterns In acute CORonary syndrome patients) study: rationale, design, and baseline characteristics. *Am Heart J* 2013;165:8-14.

12. Pocock S, Bueno H, Licour M, Medina J, Zhang L, Annemans L, Danchin N, Huo Y, Van de Werf F. Predictors of one-year mortality at hospital discharge after acute coronary syndromes: a new risk score from the EPICOR (long-term follow up of antithrombotic management patterns In acute CORonary syndrome patients) study. *Eur Heart J Acute Cardiovasc Care* 2014;4:509-517.

13. Huo Y, Lee SW, Sawhney JP, Kim HS, Krittayaphong R, Nhan VT, Alonso-Garcia A, Han YL, Ge J, Chin CT, Ong TK, Jan S, Itoh Y, Vega AM, Pocock S. Rationale, Design, and Baseline Characteristics of the EPICOR Asia Study (Long-term follow-up of antithrombotic management patterns In Acute CORonary Syndrome patients in Asia). *Clin Cardiol* 2015;38:511-519.

14. Sinnaeve PR, Zeymer U, Bueno H, Danchin N, Medina J, Sanchez-Covisa J, Licour M, Annemans L, Jukema JW, Pocock S, Storey RF, Van de Werf F. Contemporary inter-hospital transfer patterns for the management of acute coronary syndrome patients: findings from the EPICOR study. *Eur Heart J Acute Cardiovasc Care* 2015;4:254-262.

15. Huo Y, Lee SWL, Sawhney JP, Kim HS, Krittayaphong R, Nhan VT, Alonso-Garcia A, Hayashi N, Zhang L, Han YL, Ge J, Chin CT, Ong TK. Contemporary pre-hospital management of acute coronary syndromes patients: results from the EPICOR Asia study. *Circulation* 2013;128.
16. Von Hippel PT. How to impute interactions, squares, and other transformed variables. *Sociol Methodol* 2009;39:265-291.
17. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37:53-72.
18. D'Agostino RB, Nam B-H. Evaluation of the performance of survival analysis models: discrimination and calibration measures. *Handbook of Statistics* 2003;23:1-25.
19. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J* 2014;35:1925-1931.
20. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361-387.
21. Steyerberg EW. *Clinical prediction models*. New York, USA: Springer Science+Business Media, LLC; 2009.
22. Buturlin K, Minha S, Rozenbaum Z, Neuman Y, Shlezinger M, Goldenberg I, Mosseri M, Pereg D. Admission plasma glucose levels within the normal to mildly



impaired range and the outcome of patients with acute coronary syndrome. *Eur Heart J Acute Cardiovasc Care* 2016.

23. Puymirat E, Taldir G, Aissaoui N, Lemesle G, Lorgis L, Cuisset T, Bourlard P, Maillier B, Ducrocq G, Ferrieres J, Simon T, Danchin N. Use of invasive strategy in non-ST-segment elevation myocardial infarction is a major determinant of improved long-term survival: FAST-MI (French Registry of Acute Coronary Syndrome). *JACC Cardiovasc Interv* 2012;5:893-902.

24. White HD, Westerhout CM, Alexander KP, Roe MT, Winters KJ, Cyr DD, Fox KA, Prabhakaran D, Hochman JS, Armstrong PW, Ohman EM. Frailty is associated with worse outcomes in non-ST-segment elevation acute coronary syndromes: insights from the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medically manage Acute Coronary Syndromes (TRILOGY ACS) trial. *Eur Heart J Acute Cardiovasc Care* 2016;5:231-242.

25. Bueno H, Martin Asenjo R. Long-term cardiovascular risk after acute coronary syndrome, an ongoing challenge. *Rev Esp Cardiol (Engl Ed)* 2016;69:1-2.

26. Wang ZJ, Zhou YJ, Galper BZ, Gao F, Yeh RW, Mauri L. Association of body mass index with mortality and cardiovascular events for patients with coronary artery disease: a systematic review and meta-analysis. *Heart* 2015;101:1631-1638.

27. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA, Jr., Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute

coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;333:1091.

**Table 1. Descriptive statistics for key baseline variables**

	EPICOR	EPICOR Asia	NSTE-ACS	STEMI	All	Deaths (%)	Missing (%)
Total	10,567	12,922	11,930	11,559	23,489	5.5	
Age (year) mean (SD)	61.8 (12.3)	60.1 (11.6)	62.8 (11.6)	58.9 (11.9)	60.9 (11.9)		0.004
Sex							0.0
Female	2,647 (25.0)	3,065 (23.7)	3,523 (29.5)	2,189 (18.9)	5,712 (24.3)	6.6	
Male	7,920 (75.0)	9,857 (76.3)	8,407 (70.5)	9,370 (81.1)	17,777 (75.7)	5.1	
Region							0.0
China	0	8,214 (63.6)	4,253 (35.6)	3,961 (34.3)	8,214 (35.0)	4.6	
Hong Kong, Singapore, South Korea	0	975 (7.5)	553 (4.6)	422 (3.7)	975 (4.2)	3.4	
India	0	2,468 (19.1)	986 (8.3)	1,482 (12.8)	2,468 (10.5)	6.7	
Malaysia, Thailand, Vietnam	0	1,265 (9.8)	514 (4.3)	751 (6.5)	1,265 (5.4)	8.1	
Eastern Europe	2,380 (22.5)	0	1,235 (10.4)	1,145 (9.9)	2,380 (10.1)	6.3	
Latin America	2,069 (19.6)	0	1,003 (8.4)	1,066 (9.2)	2,069 (8.8)	8.8	
Northern Europe	3,781 (35.8)	0	2,173 (18.2)	1,608 (13.9)	3,781 (16.1)	3.8	
Southern Europe	2,337 (22.1)	0	1,213 (10.2)	1,124 (9.7)	2,337 (9.9)	5.5	
Education level							22.2
No formal	477 (6.5)	1,048 (9.6)	798 (8.7)	727 (8.0)	1,525 (8.3)	10.2	
Primary	2,559 (34.7)	2,974 (27.3)	2,788 (30.5)	2,745 (30.0)	5,522 (30.3)	6.9	
Secondary	3,275 (44.4)	4,739 (43.5)	3,997 (43.8)	4,017 (43.9)	8,014 (43.8)	4.2	
University	1,071 (14.5)	2,138 (19.6)	1,553 (17.0)	1,656 (18.1)	3,209 (17.6)	4.1	
Prior cardiac disease							1.9
MI	1,960 (18.8)	1,229 (9.8)	2,245 (19.2)	944 (8.1)	3,189 (13.8)	13.9	
Angina	1,233 (11.8)	1,976 (15.7)	2,392 (20.5)	817 (7.0)	3,209 (13.9)	13.9	
Heart failure	507 (4.9)	320 (2.5)	662 (5.7)	165 (1.4)	827 (3.6)	3.6	
Atrial fibrillation	497 (4.8)	188 (1.5)	498 (4.3)	187 (1.6)	685 (3.0)	3.0	
Any of the above	2,904 (27.8)	2,890 (22.9)	4,115 (35.3)	1,679 (14.8)	5,794 (25.2)	9.3	
Prior COPD/other CLD	683 (6.6)	352 (2.8)	637 (5.5)	398 (3.5)	1,035 (4.5)	13.7	1.9
BMI, kg/m <sup>2</sup> , mean (SD)	27.7 (4.4)	24.6 (3.4)	26.2 (4.3)	25.7 (4.0)	25.9 (4.1)	4.1	11.3
<20 kg/m <sup>2</sup>	156 (1.7)	806 (6.8)	448 (4.2)	514 (5.0)	962 (4.6)	11.4	
Ejection fraction at admission							7.3
Normal ≥40%	8,676 (89.4)	11,099 (92.0)	10,181 (92.7)	9,594 (88.9)	19,775 (90.9)	4.6	

Moderately reduced 30–39%	787 (8.1)	714 (5.9)	550 (5.0)	951 (8.8)	1,501 (6.9)	12.9	
Severely reduced <30%	239 (2.5)	250 (2.1)	247 (2.2)	242 (2.2)	489 (2.2)	20.9	
Diagnosis							0.0
NSTE-ACS	5,624 (53.2)	6,306 (48.8)	11,930 (100)	0	11,930 (50.8)	5.9	
STEMI	4,943 (46.8)	6,616 (51.2)	0	11,559 (100)	11,559 (49.2)	5.0	
Killip class at event							22.2
I	8,296 (87.4)	6,591 (75.0)	6,173 (82.9)	8,714 (80.4)	14,887 (81.4)	4.6	
II	834 (8.8)	1,393 (15.9)	841 (11.3)	1,386 (12.8)	2,227 (12.2)	9.4	
III or IV	367 (3.9)	802 (9.1)	431 (4.8)	738 (6.8)	1,169 (6.4)	14.5	
Interventions during admission							0.5
None	2,975 (28.2)	3,407 (26.6)	4,616 (39.0)	1,766 (15.3)	6,382 (27.3)	9.8	
PCI	6,898 (65.4)	8,757 (68.3)	6,909 (58.3)	8,746 (75.9)	15,655 (67.0)	3.8	
CABG	268 (2.5)	107 (0.8)	285 (2.4)	90 (0.8)	375 (1.6)	3.5	
Reperfusion	7,339 (69.5)	9,316 (72.7)	6,963 (58.8)	9,692 (84.1)	16,655 (71.3)	3.9	
Any of the above	7,580 (71.8)	9,406 (73.4)	7,230 (61.0)	9,756 (84.7)	16,986 (72.7)	3.8	
Serum creatinine, mg/dL, mean (SD)	1.05 (0.5)	1.10 (0.6)	1.10 (0.6)	1.06 (0.5)	1.08 (0.58)	–	4.6
Blood glucose, mg/dL, mean (SD)	143.7 (79.9)	139.6 (69.0)	135.4 (76.5)	147.7 (71.0)	141.4 (74.1)	–	12.0
Haemoglobin, g/dL, mean (SD)	14.1 (2.0)	13.7 (2.5)	13.7 (2.4)	14.0 (2.1)	13.9 (2.3)	–	5.3
<11 g/dL	434 (4.4)	975 (7.9)	825 (7.3)	584 (5.3)	1,409 (6.3)	16.0	
11–12.9 g/dL	1,788 (18.1)	3,201 (25.9)	2,777 (24.6)	2,212 (20.2)	4,989 (22.4)	7.4	
≥13 g/dL	7,654 (77.5)	8,186 (66.2)	7,692 (68.1)	8,148 (74.5)	15,840 (71.2)	3.9	
In-hospital cardiac complications							0.8
MI or recurrent ischemia	600 (5.7)	590 (4.6)	592 (5.0)	598 (5.0)	1,190 (5.1)	8.5	
Cardiogenic shock	109 (1.0)	312 (2.4)	65 (0.5)	356 (3.0)	421 (1.8)	10.7	
Heart failure	616 (5.8)	663 (5.1)	513 (4.3)	766 (6.4)	1,279 (5.5)	15.9	
Any arrhythmia	1,013 (9.6)	587 (4.6)	567 (4.8)	1,033 (8.7)	1,600 (6.8)	10.1	
Any of the above	1,943 (18.5)	1,863 (14.5)	1,550 (13.0)	2,256 (19.6)	3,806 (16.3)	10.4	
Simple EQ-5D score at discharge							2.0
0	4,774 (46.3)	8,156 (64.1)	6,437 (55.0)	6,493 (57.4)	12,930 (56.1)	3.5	
1	2,206 (21.4)	1,533 (12.1)	1,916 (16.4)	1,823 (16.1)	3,739 (16.2)	16.2	
≥2	3,333 (32.2)	3,028 (23.8)	3,358 (28.7)	3,003 (26.5)	6,361 (27.6)	27.6	
On diuretics at discharge	1,966 (18.7)	1,694 (13.2)	2,020 (17.0)	1,640 (14.3)	3,660 (15.7)	12.6	0.5
On aldosterone inhibitor at discharge	898 (8.5)	1,019 (7.9)	733 (6.2)	1,184 (10.3)	1,917 (8.2)	12.7	0.5

BMI, body mass index; CABG: coronary artery bypass graft; CLD, chronic lung disease; COPD: chronic obstructive pulmonary disease; EQ-5D, EuroQol; MI, myocardial infarction; NSTEMI: non-ST-elevation acute coronary syndrome; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-segment elevation myocardial infarction.

**Table 2. Multivariate analysis of 2-year mortality: final model for all patients**

Variable	Risk coefficient	HR	95% CI	P
Age (per 10 years)	0.42	1.52	1.44–1.61	<.00001
Ejection fraction <sup>a</sup>				
<40%	0.57	1.77	1.50–2.09	<.00001
<30%	0.87	2.40	1.93–2.98	
No coronary revascularisation or thrombolysis	0.58	1.79	1.58–2.02	<.00001
EQ-5D score at discharge				
1	0.22	1.24	1.16–1.33	<.00001
≥2	0.43	1.54	1.35–1.77	
Previous cardiac disease	0.34	1.41	1.24–1.59	<.00001
Prior COPD/other CLD	0.45	1.57	1.31–1.88	<.00001
Serum creatinine (per log unit if ≥1.2 mg/dL) <sup>a,b</sup>	0.66	1.94	1.63–2.32	<.00001
Blood glucose (per 100 mg/dL if ≥140 mg/dL) <sup>a,c</sup>	0.19	1.21	1.12–1.32	<.00001
Haemoglobin <sup>a</sup>				
<13 g/dL	0.24	1.27	1.10–1.45	<.00001
<11 g/dL	0.60	1.82	1.52–2.18	
On diuretics at discharge	0.30	1.35	1.17–1.55	<.0001
On aldosterone inhibitor at discharge	0.29	1.34	1.14–1.58	.0005
Male sex	0.28	1.32	1.15–1.51	<.0001

Education				
No formal	0.00	1.00	–	
Primary	–0.14	0.87	0.80–0.93	.0002
Secondary	–0.29	0.75	0.65–0.87	
University	–0.43	0.65	0.52–0.82	
In-hospital cardiac complications	0.22	1.25	1.09–1.42	.0009
BMI <20 kg/m <sup>2</sup>	0.36	1.43	1.16–1.77	.0009
Diagnosis of STEMI	0.20	1.22	1.07–1.38	.002
Killip class				
I	0.00	1.00	–	
II	0.18	1.19	1.01–1.41	.004
III–IV	0.32	1.38	1.14–1.67	
Country/region				
China	0.00	1.00	–	
Hong Kong, Singapore, South Korea	–0.50	0.60	0.42–0.87	
India	0.10	1.05	0.83–1.32	
Malaysia, Thailand, Vietnam	0.05	1.10	0.90–1.35	
Eastern Europe	0.21	1.24	1.01–1.51	<.00001
Latin America	0.36	1.44	1.19–1.73	
Western Europe (North)	–0.33	0.72	0.59–0.88	
Western Europe (South)	–0.11	0.89	0.72–1.10	

BMI, body mass index; CI, confidence interval; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; STEMI, ST-segment elevation myocardial infarction.

Risk coefficient =  $\ln(\text{HR})$

<sup>a</sup>during admission.

<sup>b</sup>example, for creatinine 3.26 mg/dL [ $\log(3.26) = \log(1.2) + 1$ ] HR is 1.98 compared with creatinine  $\leq 1.2$  mg/dL.

<sup>c</sup>example, for glucose 240 mg/dL HR is 1.21 compared with glucose  $\leq 140$  mg/dL.



**Table 3. Multivariate analysis of 2-year mortality: final model separated by diagnosis**

	NSTE-ACS		STEMI	
Variable	HR	95% CI	HR	95% CI
Age (per 10 years)	1.55	1.43–1.67	1.51	1.39–1.64
Ejection fraction <sup>a</sup>				
<40%	1.89	1.50–2.38	1.65	1.30–2.10
<30%	2.28	1.69–3.08	2.72	1.96–3.77
No coronary revascularisation or thrombolysis	1.83	1.56–2.16	1.72	1.42–2.07
EQ-5D score at discharge				
1	1.19	1.09–1.30	1.30	1.18–1.44
≥2	1.42	1.18–1.70	1.69	1.39–2.06
Previous cardiac disease	1.32	1.12–1.55	1.54	1.26–1.86
Prior COPD/other CLD	1.80	1.44–2.25	1.23	0.89–1.70
Serum creatinine (per log unit if ≥1.2 mg/dL) <sup>a,b</sup>	1.98	1.58–2.48	1.89	1.40–2.55
Blood glucose (per 100 mg/dL if ≥140 mg/dL) <sup>a,c</sup>	1.26	1.12–1.42	1.16	1.02–1.31
Haemoglobin <sup>a</sup>				
<11 g/dL	1.88	1.48–2.39	1.79	1.36–2.34
<13 g/dL	1.35	1.12–1.63	1.18	0.96–1.46
On diuretics at discharge	1.30	1.08–1.57	1.36	1.09–1.68
On aldosterone inhibitor at discharge	1.49	1.18–1.88	1.23	0.97–1.57
Male sex	1.39	1.17–1.66	1.23	1.00–1.52
Education				
No formal	1.00	–	1.00	–
Primary	0.85	0.77–0.94	0.89	0.79–0.99
Secondary	0.73	0.59–0.89	0.78	0.63–0.98
University	0.62	0.46–0.84	0.70	0.50–0.97

In-hospital cardiac complications	1.27	1.06–1.53	1.23	1.02–1.49
BMI <20 kg/m <sup>2</sup>	1.34	0.99–1.81	1.58	1.18–2.12
Killip class				
I	1.00	–	1.00	–
II	1.07	0.84–1.35	1.33	1.06–1.19
III–IV	1.27	0.96–1.67	1.54	1.18–1.99
Country/region				
China	1.00	–	1.00	–
Hong Kong, Singapore, South Korea	0.77	0.49–1.21	0.43	0.23–0.79
India	1.06	0.77–1.44	1.08	0.83–1.41
Malaysia, Thailand, Vietnam	1.32	0.97–1.80	0.81	0.57–1.15
Eastern Europe	1.47	1.12–1.92	1.02	0.75–1.38
Latin America	1.59	1.22–2.06	1.29	0.99–1.70
Western Europe (North)	0.84	0.64–1.09	0.58	0.41–0.82
Western Europe (South)	1.05	0.80–1.39	0.73	0.52–1.01

BMI, body mass index; CI, confidence interval; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; NSTEMI: non-ST-elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction.

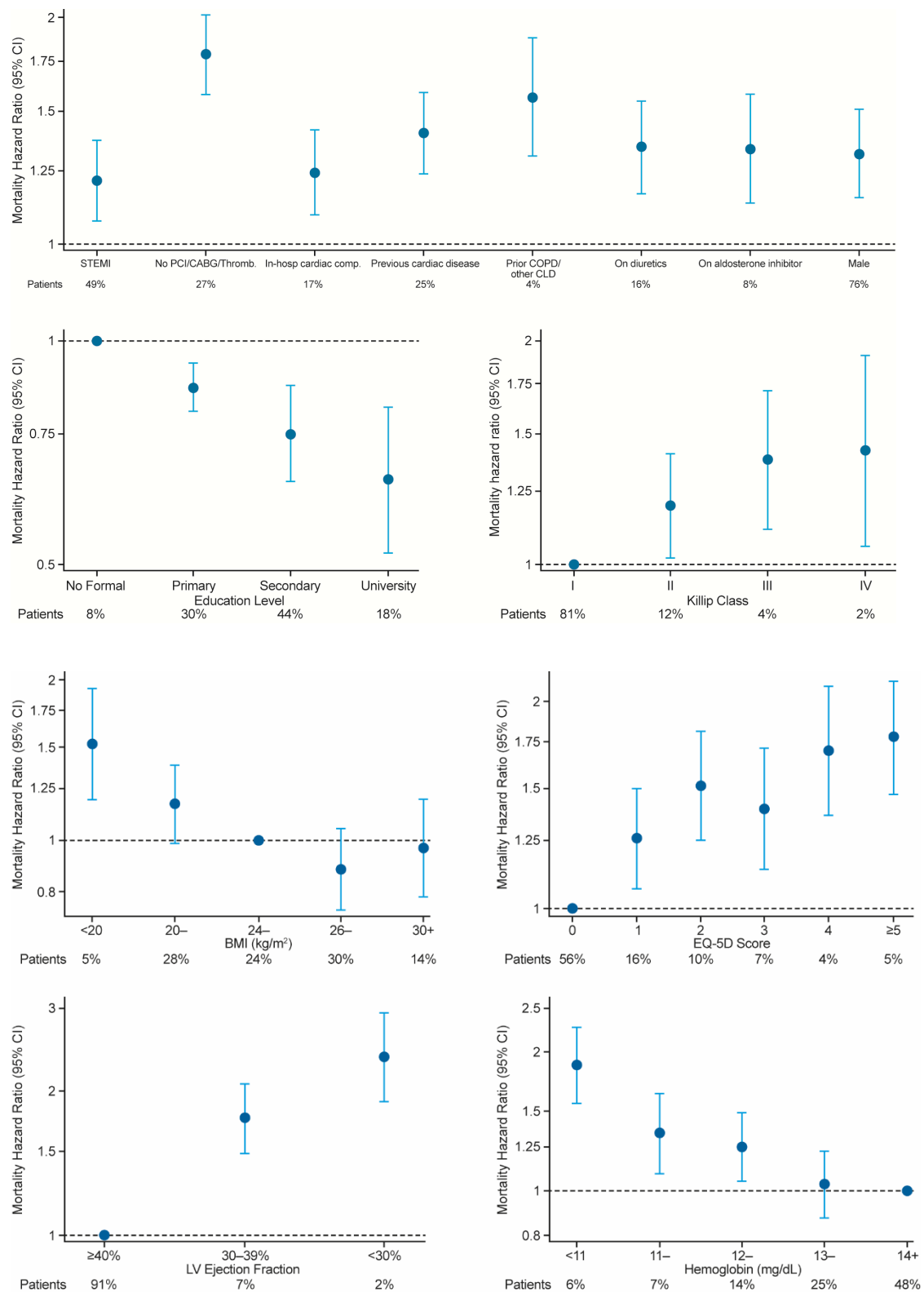
<sup>a</sup>during admission.

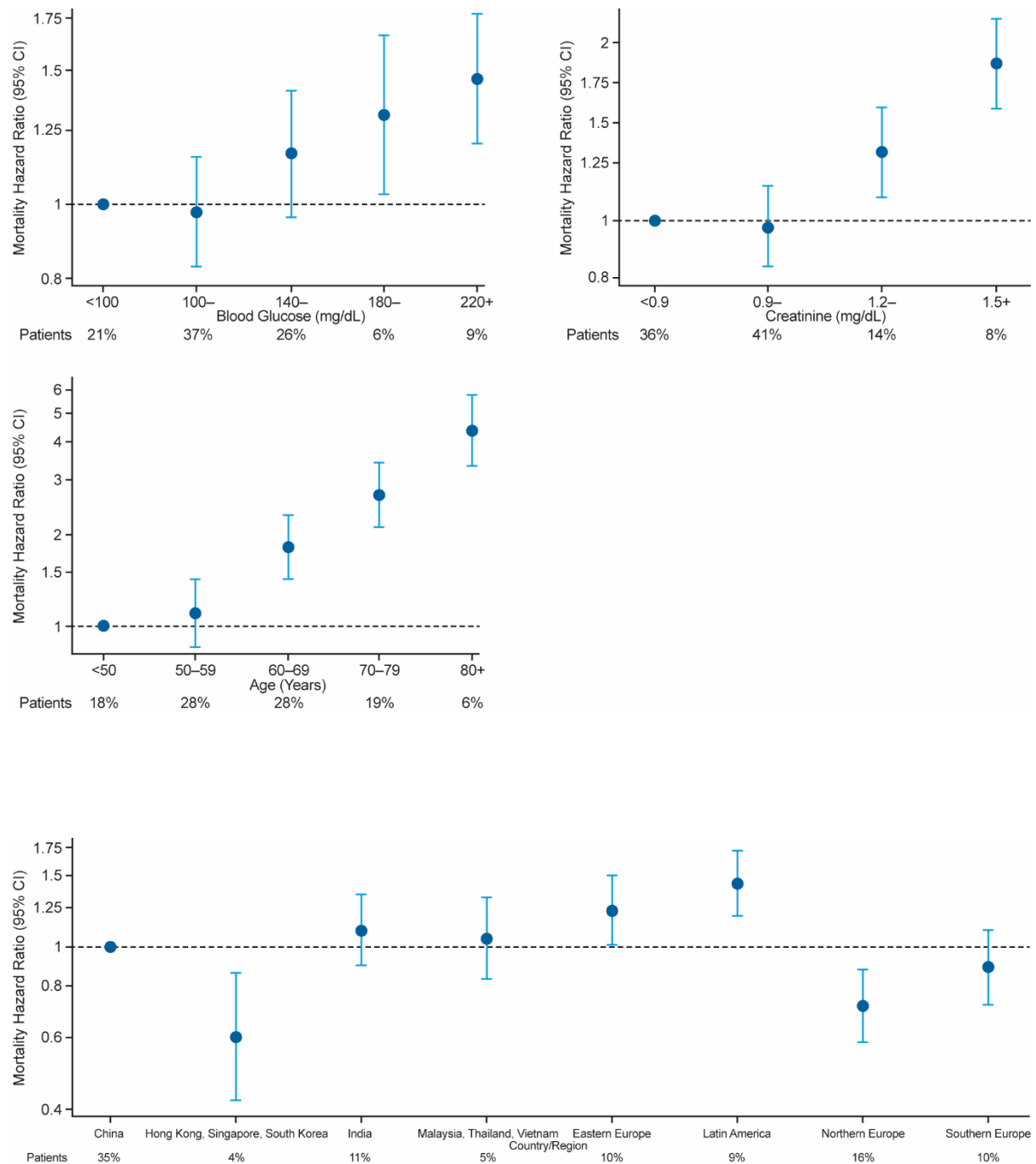
<sup>b</sup>example, for creatinine 3.26 mg/dL [ $\log(3.26) = \log(1.2) + 1$ ] HR is 1.98 compared with creatinine  $\leq 1.2$  mg/dL.

<sup>c</sup>example, glucose 240 mg/dL HR is 1.21 compared with glucose  $\leq 140$  mg/dL.

For every variable, comparison of HR values for STEMI and NSTEMI respectively, revealed no evidence of a statistical interaction;  $P > .05$  for all interaction tests performed.

**Figure 1. Mortality hazard ratios for each variable in the predictive model**

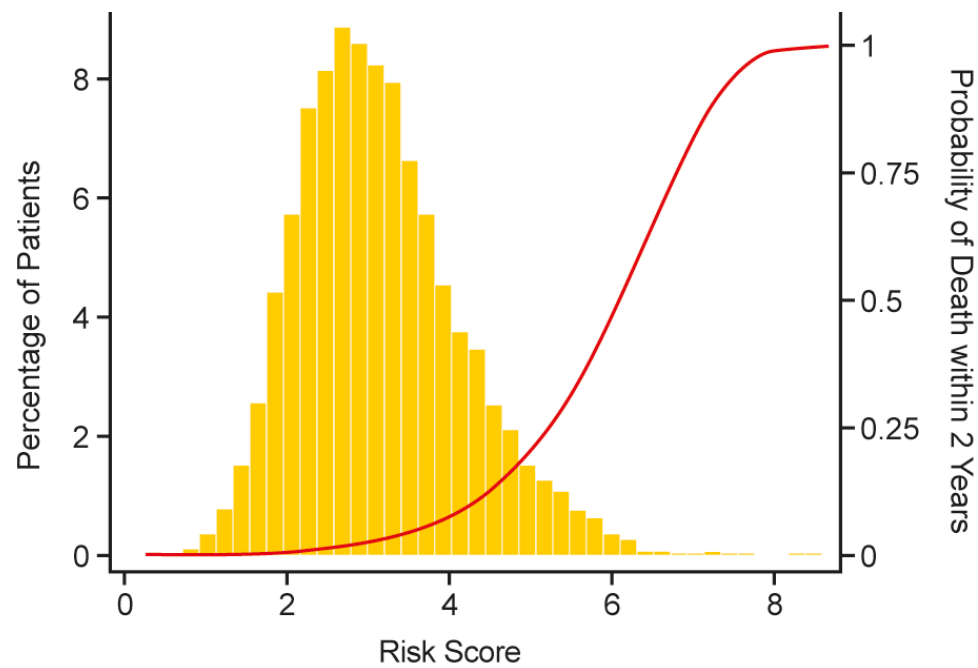




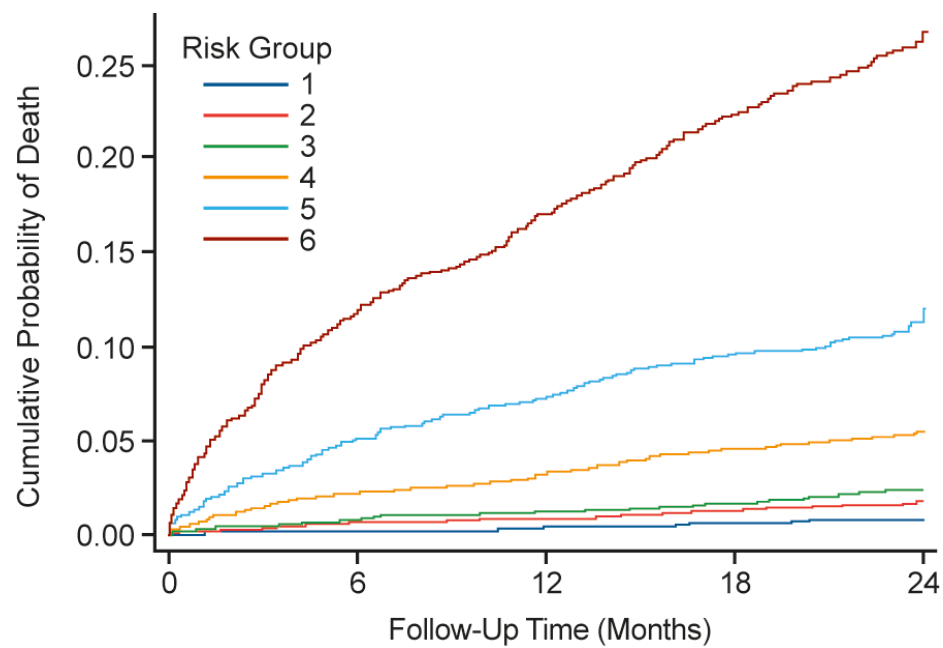
BMI, body mass index; CABG, coronary artery bypass graft; CI, confidence interval; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; EQ-5D, EuroQol; LV, left ventricular; NSTEMI, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction.

**Figure 2. (A) Risk score distribution and predicted mortality risk, (B) Cumulative mortality and (C), Risk discrimination and model goodness-of-fit**

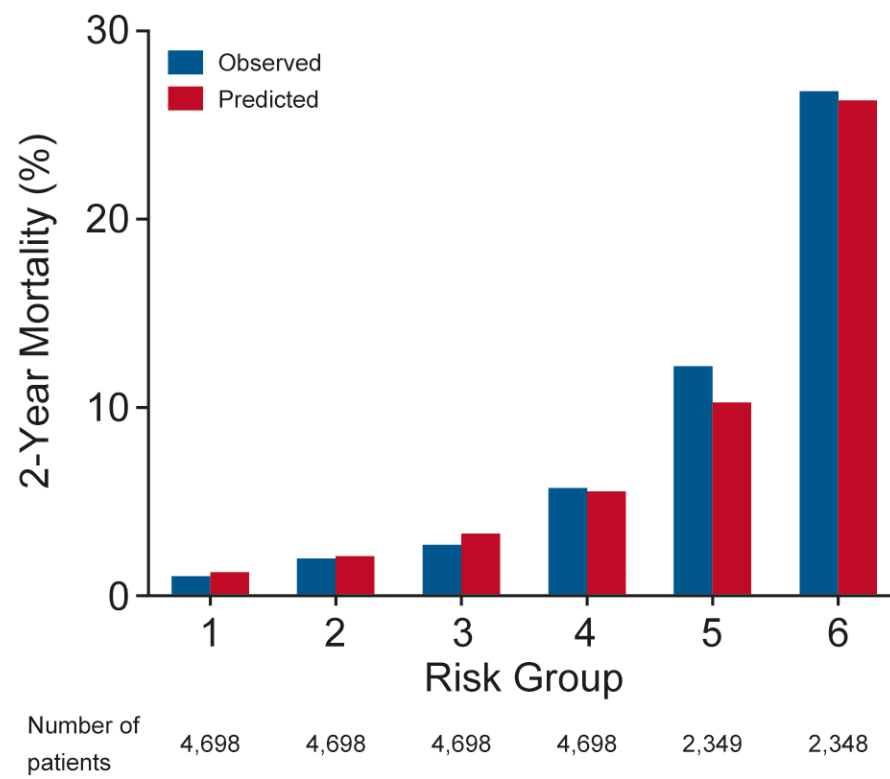
**A**



**B**



**c**



Panels B and C'; risk groups 1–4 correspond to quintiles 1–4, with the fifth quintile subdivided into 2 deciles (risk groups 5 and 6).